Improving consistency for a Mefenamic acid immediate release formulation

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Introduction

Mefenamic acid (MFA) product performance is highly dependant on particle size and can lead to variable efficacy.

In this study, a structured development program was applied, developing a crystalline solid dispersion (CSD) formulation, retaining API properties and improving performance consistency compared to a commercial product.

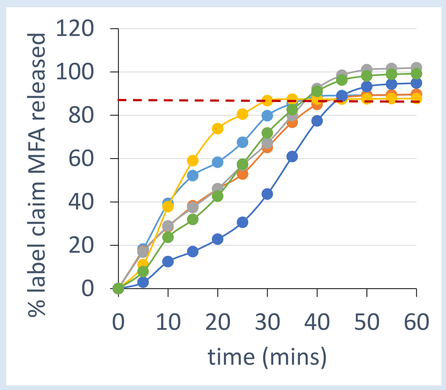

Figure 1: USP II dissolution test (pH 9) of 250mg MFA capsules, Pharmavit Limited (PVL), Batch 4348: red dashed line 85% drug release.

	HUB target product profile
Dose form	Oral solid dose form
Dose	250 mg Mefenamic acid (MFA)
Release profile	• IR release profile, controlled via particle size • Consistent performance
Formulation	Crystalline solid dispersion (CSD)
Process	HME – 3D print/ injection mould
Predictive approach	Rheology screening tool to predict HME process parameters

Table 1: HUB acid target product profile.

Rheology screening

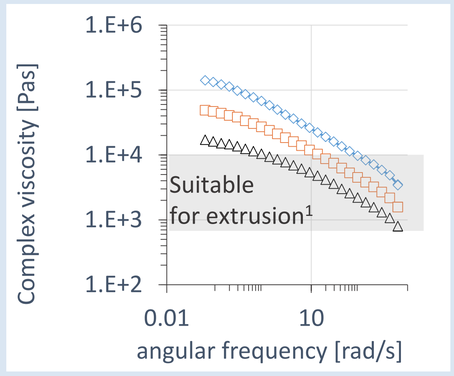

Figure 2: Complex viscosity versus angular frequency for Soluplus +15% w/w Sorbitol (SOL15) at 120°C (blue), 130°C (orange) and 140°C (black).

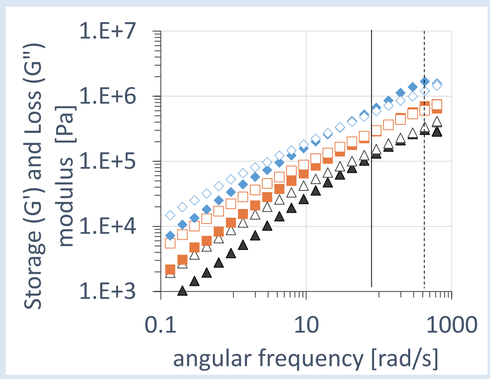

Figure 3: Storage (filled) and Loss (open) modulus versus angular frequency for SOL15 at 120°C (blue), 130°C (orange) and 140°C (black).

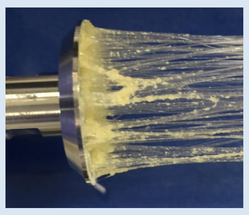

Figure 4: 50% w/w MFA in SOL15SORB after rheology test

Predicted HME process temperature: 132°C

Dominating viscoelastic properties with angular frequency ↑ :

- **viscous (G") >140°C**
- **elastic (G') <130°C**

Screening failed >20% w/w

Hot-melt-extrusion

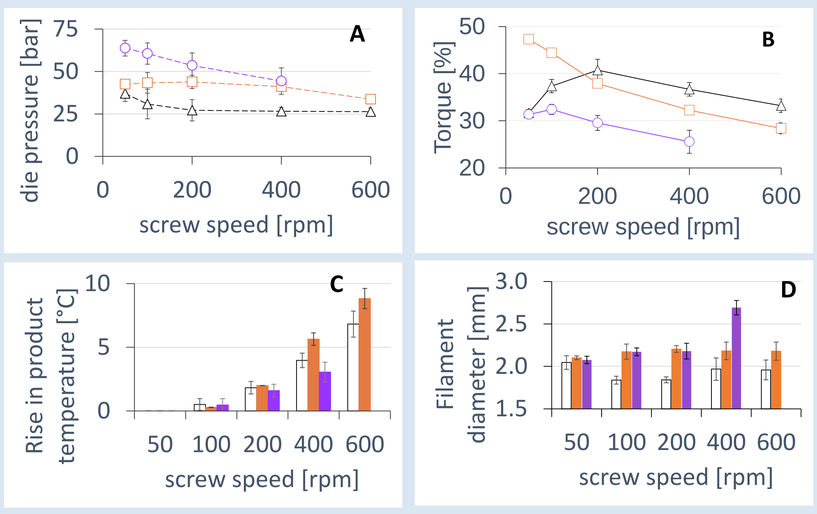

Figure 5:
HME process data.
A) Die pressure,
B) Torque,
C) Rise in product temperature and
D) Filament diameter versus screw speed:
SOL15: black-140°C, orange-130°C;
50MFA-SOL15: purple-125°C.

Lowest HME process Temperature:

SOL15: 130°C

50MFA-SOL15: 125°C

Product temperature ↑:

SOL15 130°C > 140°C

Die swell SOL15: 130°C > 140°C

Product characterisation

Figure 6: HME extruded filaments: top **50MFA-SOL15**, bottom **SOL15**.

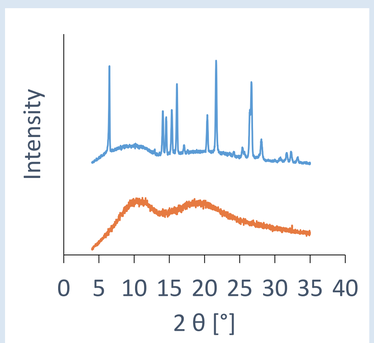

Figure 7: XRPD data of extrudates: top **50MFA-SOL15**, bottom **SOL15**.

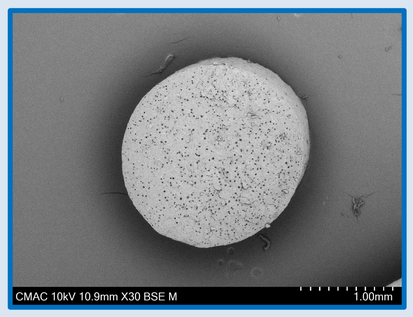

Figure 8:
SEM image of **50MFA-SOL15** and **SOL15** extrudates.

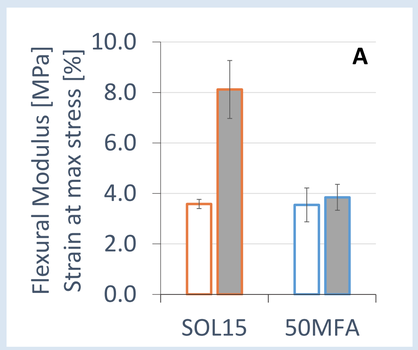

Figure 9: Mechanical properties of **50MFA-SOL15** and **SOL15**. extrudates: A) Flexural modulus, Strain at max stress, B) Max stress and Modulus of toughness (MoT).

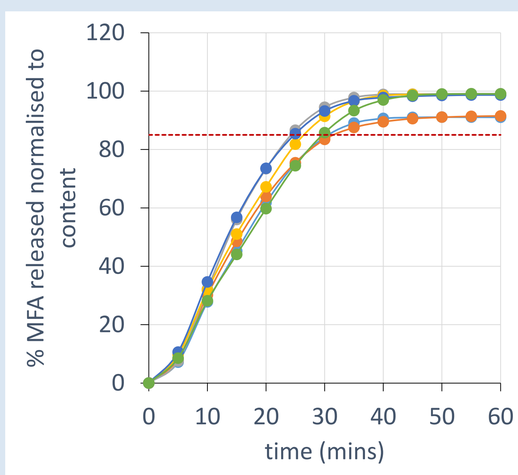

Figure 10: USP II dissolution test (pH 9) of 250mg MFA capsules with **50MFA-SOL15 extrudate**. red dashed line 85% drug release.

Conclusion

Rheology guided process development was successful, but also highlights the limitations of this technique.

The targeted immediate release profile for the CSD of MFA in Soluplus®-Sorbitol formulation has been met, whilst the stable crystalline form (I) of MFA has been retained and the consistency of drug release has been significantly improved.

References:

1) Kolter K, Karl M, Gryczke A. 2012. Hot-Melt Extrusion with BASF Pharma Polymers. 2nd Revised and Enlarged Edition ed., Ludwigshafen, Germany: BASF The Chemical Company

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